

# Pharmacogenetics: Mismatches Between Policy and Practice

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**Abstract**— Pharmacogenetics (PGx) and personalised medicine are new disciplines that, gathering the existing knowledge about the genetic and phenotypic factors that underpin drug response, aim to deliver more targeted therapies that avoid the existing problems of adverse drug reactions or lack of drug efficacy. These disciplines imply a shift in the way drugs are prescribed, as they require introducing diagnostic tools and implementing pre-screening mechanisms that assess patients' susceptibility to new or existing drugs. The direct benefit is an improvement in drug safety and/or efficacy. However, neither PGx nor personalised medicines are widely used in clinical practice. They both face a series of gaps in knowledge that hamper their widespread use in clinical practice.

This paper illustrates, through the case of TPMT (thiopurine methyltransferase) testing for preventing adverse events caused by the drug azathioprine, how the use of personalised medicine is being shaped by user-producer mechanisms and negotiated between different actors involved in the process of drug development and service delivery. The paper uses concepts of the sociology of science and a qualitative approach to explore the existing mismatches between PGx policy and practice.

**Index Terms**— *diffusion of innovation in health service organisations, demand-driven innovation, drug reimbursement, NICE, pharmacogenetics, personalised medicine.*

## I. INTRODUCTION

Pharmacogenetics (PGx) and personalised medicine are new approaches to health care. They focus on the study of the differences in drug response among groups of individuals who share common genetic/phenotypic characteristics [1]. These characteristics determine how group of individuals respond to drugs, in terms of efficacy and toxicity [2].

PGx and personalised medicine emerged as technologies that followed either of two technological trajectories [3]: improvements in the understanding of disease and drug response through better approaches to drug target discovery and drug development [4], or new drug-test associations to improve the safety and efficacy of both licensed drugs and drugs under development [5, 6]. Either case requires the integration of genetic/phenotypic tests that act as companion diagnostics for specific drugs.

An adequate companion diagnostic is designed to provide relevant information about the drug it is targeted for. The correct drug-diagnostic association can avoid adverse drug reactions (ADRs), or can target drugs to sub-populations of good responders (populations defined by genetic or phenotypic features). The direct benefit is an improvement in drug safety and/or efficacy.

Pharmaceutical companies, during pre-clinical studies, search for molecular biomarkers that have a potential use in the drug development process. These molecular biomarkers are susceptible to be transformed into effective diagnostics if an adequate drug-test association is demonstrated. The use of pharmacogenetics to improve drug safety is particularly important in the current environment, where drug regulations are becoming more stringent. Despite increased R&D investments, since the mid-1990s, the pharmaceutical industry has seen a decline in the number of chemical entities to market [7]. Between 1998 and 2002, the average annual number of new drugs approved by the FDA was 68; by 2003, this number had dropped by two-thirds. In 2004 the number of approved drugs was 21 [8]. Any new medicinal compound entering Phase I clinical trials have only an estimated 8% chance of reaching the market [9] and, even after doing it, drugs can be withdrawn because of safety concerns. From 1990 to 2006, 38 drugs were withdrawn from major markets due to safety problems [10].

The use of pharmacogenetics to improve the safety of drugs already marketed might be of benefit to patients but of less interest to the pharmaceutical industry, in particular if these drugs are not covered by patent protection [11, 12].

However, either if PGx is used to improve drug safety or if it is used to improve efficacy, its benefits are not yet fully translated into clinical practice. Taking into consideration the potential molecular biomarkers that might determine drug response, there are only a number of validated diagnostics that are eligible to be used in combination with a drug.

This paper uses an innovation perspective to propose that, some of the reasons why pharmacogenetics and personalised medicine are not widely used in clinical practice are due to, not only clinical determinants but also existing mismatches between issues at a high policy level and issues at the level of implementation.

## II. MEDICAL INNOVATIONS, DIFFUSION AND ADOPTION

The exploitation of new knowledge-intensive technologies is a long and contested process that would not occur if it did not represent an opportunity for industry and markets [13]. Industry seeks competitive advantage from the exploitation of new inventions (innovations when they are commercially available); however, new inventions and innovations are highly unstable because, when they reach the market, they face numerous constraints (technical, cultural, economic, ethical and regulatory) [14]. The initial uses that innovators anticipate for their inventions are often frustrated because, in order for these to be adopted, they need to be adapted and re-shaped to fit within an existing socio-economic environment. In pharmaceutical development this environment is determined, to a great extent, by health organisations, national boundaries, institutions and regulations, communities of practitioners and patient organisations.

Medical innovations are heterogeneous. They can involve therapeutics (targeted at preventing or combating disease) or diagnostics (aimed at assessing susceptibility to disease or drug response). Some technologies are more invasive than others, some involve testing the blood and others, testing the genes and not all raise the same regulatory and ethical concerns. Medical innovations, also, differ from any other innovation source in its high degree of regulations, both at the point of development and delivery. This is a reason why, the diffusion and adoption of a medical technology or health intervention, requires a deep understanding of the socio-political environment that drives health policy and practice [15].

Thomas Hughes uses the term socio-technical system to illustrate the co-evolution of “*the social*” and “*the technological*”, and represents the history of evolving socio-technical systems in different phases [16]: invention, development, innovation, transfer and growth, competition and consolidation. These phases are not sequential, they overlap and backtrack, and so, after invention, development and innovation, there is more invention. Innovation is, therefore, a process of social interaction among users, producers, regulators and the public, which leads, in the case of medicine, to incremental changes in equipment, techniques, drugs or guidelines that induce further changes that define scientific and technological trajectories [17].

Some of the incremental changes that contribute to the radical outcome in PGx refer to scientific advances in genomics research, to the development of associated genomic technologies and their use during drug development, to the setting-up of testing facilities in hospitals and to their inclusion into routine clinical practice. This needs to be accompanied by enough clinical evidence to support the clinical utility of new drugs; by cost-effectiveness studies that ensure compliance with existing reimbursement policies; by clinical guidelines that guarantee adequate standards of practice; and by ethical and regulatory frameworks that assure the safety and confidentiality of PGx and personalised therapies.

## III. PHARMACOGENETICS AS A SOCIO-TECHNICAL SYSTEM

Some sociologists of science explain the diffusion of technologies in terms of socio-technical networks formed by human and non-human actors, who hold conflicting positions and align them in an effort to stabilise an emerging network [18]. This alignment of conflicting interests requires a process of negotiation and compromise during which some technological trajectories are accepted and others are rejected [19]. Some authors explain this process as a socio-technical evolution or co-shaping mechanism in which different actors start favoring particular trajectories and begin to shape the direction of the technology towards these [20], generating strong path-dependencies that marginalize competing technologies [14]. This is an indication that, technological innovation cannot be understood without framing it in the particular socio-economic context in which it emerges, it is used and it dies. The inclusion of technology into more general accounts, requires that the technological, the economic, the political, the social and the natural, are seen as interrelated [21].

A socio-technical systems perspective allows the understanding of technology development and use in terms of a complex adaptive processes constituting the interdependencies between the material and the social [22]. The functioning of socio-technical systems results as an outcome of the activities of human actors embedded in social groups that share certain characteristics, perceptions, problem-agendas, norms, preferences and the like. For this reason, socio-technical systems are multi-

dimensional [23] and focus, not only on innovations but on functionality, encompassing the production, diffusion and use of the technology.

The process of invention, innovation and technological diffusion in health care (or also translational research or technology transfer) brings together different actors: the drug industry, health care providers, researchers, clinicians, patients, regulators and policy makers. These, together with the unexpected events or contingencies that innovation in medicine faces (e.g. drug failures, adverse events, malpractice suits; that cannot be explained exclusively through medical actions) [24], constitute a socio-technical network, formed at the same time by different sub-systems,

For the purpose of this study, the socio-technical network that underpins the development and use of pharmacogenetics in clinical practice has been defined by the following: the National Science and technology System, where public laboratories doing basic research in PGx and associated technologies are placed; the Health Delivery System, through which drugs and testing services are delivered. Linking sub-systems, the pharmaceutical and biotechnology companies, who invest in R&D projects that have an origin in public basic research. These companies will then deliver new products to the health care system. Finally, the regulatory system controls how drugs and pharmacodiagnostic tests are developed (focusing in their safety and analytical validity), how they are reimbursed and delivered, taking into account clinical utility measures that include cost-effectiveness studies among others.

The four sub-systems are interlinked (as shown in *figure 1*): The National Science and Technology System cut across the pharmaceutical and biotechnology industries, as well as across the Health Delivery System; The Regulatory System comprises both the development of drugs and pharmacodiagnostic tests, and the delivery of these through the Health System. Finally, institutions such as the Department of Health lie in the intersection of all the subsystems, since they are involved in the whole process of development and delivery of health services.

This socio-technical network will set the ground for the study of how pharmacogenetics is being used in clinical practice.

#### **FIGURE 1**

#### **IV. USER-PRODUCER INTERACTIONS**

If the previous sections discussed existing socio-technical interactions within a medical system, the focus here lies in the dynamic nature of these interactions and the feedback mechanisms that occur during the translation of medical technologies from research to delivery.

While evolutionary economics and business studies tend to focus on the production-side and the creation of knowledge and innovation, with less attention to the user side; innovation studies, more recently focused their attention on the co-evolution of technologies and markets [25].

Von Hippel proposed that the process of innovation is distributed across users, manufacturers, suppliers and others, highlighting the importance of shifting from manufacturers-as-innovators into user-producer interactions as a source of innovation [26]. These user-producer interactions control the survival of new technological artefacts in the market and ensure a demand for them [27]. In medicine, these user-producer interactions translate into clinicians prescribing drugs, patients experiencing ADRs and reporting them to the clinician, clinicians feeding back this information to regulatory agencies, regulatory agencies informing the manufacturer and the manufacturer taking the necessary actions.

After a drug has been licensed, once distributed, it may originate unexpected adverse events not detected during clinical trials. Even if a drug license justifies safety and efficacy, this evidence relies on limited information gathered during clinical trials and extrapolated to the overall population. For this reason, drug regulatory agencies, together with the drug manufacturers have established post-marketing surveillance mechanisms that track possible ADRs not detected during clinical trials. It is here when incremental improvements after adoption play an important role in pharmaceutical development and market access.

The diffusion of medical innovation, therefore, responds to a series of interactions and feedback mechanisms between the users and the developers of a technology, with the demand and supply forces determining these feedback processes [28]. According to this, policy makers regulate three types of decision-makers in the pharmaceutical market: patient and doctors on the demand side and the manufacturing industry on the supply side [29].

Ideally, efficient health systems should encourage patients to use products that are relatively cost-effective and have an established evidence base and clinicians to use guidelines to aid prescribing. However, the process of diffusion of medical innovation is heavily contingent and exposed to issues that are difficult to anticipate. This is particularly complicated in the case of pharmacogenetics, which requires two technologies (drug and test) that are often developed by different companies and are not

regulated under the same frameworks (in Europe the EMEA only regulates drugs and not diagnostics). The situation becomes even more complicated when

Some of the issues that underpin this complexity and the slow rate of implementation of PGx and personalised medicine will be illustrated through the case of TPMT testing in the UK. The case of TPMT will also serve to identify policy gaps and illustrate how current PGx policy for off-patent drugs is being shaped.

#### V. TPMT TESTING AND THE PREVENTION OF ADRs CAUSED BY AZATHIOPRINE AND 6-MERCAPTOPURINE IN THE UK

Thiopurines (Azathioprine-Imuran® and 6-Mercaptopurine-Purinethol®) are immunosuppressant drugs used, since they were first marketed in the late 1950s by Wellcome (later on Glaxo and now GSK), for treating patients undergoing organ transplant surgery. Although these drugs were firstly aimed at avoiding transplant rejection, they were later on used to treat autoimmune conditions, mainly in dermatology, rheumatology, and gastroenterology; in haematology to treat acute lymphoblastic leukaemia. Patents for both drugs are expired. The price of azathioprine in the UK ranges from £6.67 (25 mg 28-tablets pack) to £5.56 (50 mg, 56-tablets pack). 6-Mercaptopurine costs £22.54 (50 mg, 25-tablets pack)

Thiopurines, as well as any other drugs, have associated side-effects, principally a reduction in the production of white blood cells (neutropaenia) that can seriously compromise the patient's health. Patients treated with these drugs need to be monitored on a weekly basis through full blood count, liver function tests and electrolyte measurements (standard therapy), until the treatment is stabilised.

Some of the adverse drug reactions (ADRs) caused by thiopurines have been associated with low levels of or the lack of the enzyme Thiopurine Methyltransferase (TPMT) [30, 31]. According to the levels of the enzyme in the blood, people can be advised not to take the drug or be prescribed a lower dose.

The response to azathioprine has also a genetic component and, mutations in the gene that codes for TPMT can also be associated with ADRs [31-33]. However, at present, looking at the enzyme levels is, in most cases, the most used approach (with the exception of leukaemia patients undergoing blood transfusion). Mutation tests take longer and involve an analysis of the four most common mutations influencing drug response, but not all. In addition, the results of a randomized controlled trial that compares TPMT genotyping and standard care versus standard care alone concludes that there is no difference in stopping azathioprine due to an adverse reaction between the two study arms [34].

The major benefit of TPMT testing (phenotypic test) is diagnosing who is at risk of a severe ADR which may be fatal. It is estimated that only 0.3% of the population might be exposed to that level of risk; 10% of the population might be at a moderate risk (not as severe) and the remaining 90% may develop a normal drug response. The major controversy around TPMT testing is implementing a test from which, potentially, 0.3% of the population could benefit fully (from a severe even that may be fatal) and 10% could benefit partially (from a reduction in drug dose that will be better tolerated).

TPMT testing is commercially available in the US (by the company *Prometheus*) but not in the UK. In the UK there are two reference NHS laboratories that offer TPMT testing to any physician who requires the service. The cost of the TPMT service is £27 per sample. This includes doing a phenotypic analysis and, if this is not adequate or needs follow-up, also undergoing a genetic test. TPMT testing in the UK does not comply with the In Vitro Diagnostics (IVD) Directive that rules the marketing of commercial diagnostic tests, but rather, it is offered as laboratory developed or "home-brew" test.

The use of TPMT testing is not extended across the clinical community [35]; however, even though TPMT has not been added to the license of azathioprine and 6-mercaptopurine, there is a significant clinical uptake [36].

The patterns of use differ between dermatologists, rheumatologists, gastroenterologists and haematologists [37]. The British Society of Dermatologists has recommended TPMT testing before prescribing azathioprine [38], recommendation that was followed by some rheumatologists [37]. The British Society of Gastroenterologists, on the other hand, has not adhered to this decision arguing that azathioprine has been widely used in Ulcerative Colitis and Crohn's Disease and has been proved to be safe enough without the need for testing [39]. Haematologists treating acute lymphoblastic leukaemia in children have been undertaking TPMT testing as part of the UKALL (UK Acute Lymphoblastic Leukaemia) trial.

TPMT testing has probably been the test cited as having the most robust evidence to support its clinical utility [40], however, as it has been illustrated above, there is no consensus on implementation. This might be due to the lack of prospective clinical data to support a robust cost-effective case [40], but also to the regulatory gaps that exist within reimbursement policies. One of the main issues that emerged from this case study is the impact of NICE on clinical decisions, but more importantly, the impact of other factors in the lack of NICE guidelines.

## VI. THE CONTEXT OF HEALTH SERVICE DELIVERY

### A. NICE, Clinical Utility and NHS Reimbursement Policies

All healthcare systems share the same policy objectives relating to pharmaceuticals: expenditure control, efficient use of products and equitable access to them. But resources available for healthcare are limited and, controlling these is a matter of concern both in tax funded as well as in private health systems [29].

The translation of any drug or instrument into clinical practice requires compliance with three criteria: the technical accuracy of the drug or device (analytic validity), its clinical sensitivity and specificity (clinical validity), and its potential for improving health outcomes (clinical utility). There is no a clear definition of clinical utility. However, the term is commonly used as a synonym for clinical sensitivity, a term that is a combination of clinical effectiveness and/or economic evaluation, accounting also for the practitioners' perspectives about the usefulness, benefits, and drawbacks of the innovation for their working practice [41]. Other factors that are also taken into consideration when deciding whether a drug or device should be used in the clinic include: how severe the disease they intend to treat is, which treatments are already available, how accessible testing is, and other ethical, social and legal implications associated with its use [4].

In addition to this, countries apply some sort of rationing in regard to pharmaceuticals and health interventions. For products to be reimbursed by purchasing agencies, regulators require companies to provide evidence of relative effectiveness and efficiency.

Regulations governing the use of cost-effectiveness evidence in reimbursement decisions were first introduced in 1993 by the Australian Pharmaceutical Benefits Scheme. In 1994, the Canadian region of Ontario also introduced guidelines for the economic evaluation of drugs. NICE emerged in 1999 to provide evidence-based guidelines through health technology assessments and cost-effectiveness studies, to an extent to which the use of innovative drugs and technologies are controlled by NICE (through its national guidance and clinical guidelines) and NHS Trusts are heavily bound by them.

NICE has a pragmatic view on how its decisions should be made. Focusing on evidence, NICE uses a standard and internationally recognised method to compare different drugs and measure their clinical effectiveness: the quality-adjusted life year's measurement (the "QALY"). A QALY gives an idea of how many extra months or years of life of a reasonable quality a person might gain as a result of treatment (particularly important when considering treatments for chronic conditions). Cost-effectiveness is expressed as "£ per QALY", with an economic benchmark for reimbursement being no more £30,000 per QALY [42].

NICE undertakes appraisals of new and established "innovative" technologies as requested by the Department of Health, who refers technologies based on the following criteria [43]: significant health benefit, impact on health-related government policies or NHS resources, inappropriate variation in the use of the technology across the country or an added value by issuing national guidance. TPMT testing does not lie in either of the above categories.

The narrative of cost-evidence used by NICE, contrasts with the narrative of politics that applies in the particular case of azathioprine prescription and use of TPMT testing.

### A. Shaping Clinical Practice: TPMT testing in the lack of NICE Guidelines

TPMT testing emerged as a tool to predict adverse events originated by two off-patent drugs: AZA and 6-MP. The drugs cost from £5 to £22 a month; the test, £27 per patient. Both AZA and 6-MP are reimbursed by the NHS because both had been in use before NICE started appraising technologies and also, because they are relatively cheap. TPMT Testing is not reimbursed, but even though, the two National Reference Laboratories undertaking TPMT Testing have optimised prices to make a pharmacogenetics service affordable for the NHS. As a result, some NHS Trusts have implemented the use of TPMT testing locally and also, some clinical associations have formalised recommendations on TPMT testing [37].

TPMT testing varies across specialties. During the first year of the TPMT service being provided by Birmingham City Hospital, the TPMT referrals came from the following clinical specialties: gastroenterology (66.7%), dermatology (13.6%), rheumatology (12%) and other miscellaneous (7.7%) [44], with demand increasing in the following years. By diseases treated, TPMT testing was undertaken for: Crohn's Disease (27.5%), Ulcerative Colitis (31.9%), Inflammatory Bowel Disease: (4.8%), Systemic Lupus Erythematosus (4.4%), Dermatitis/Eczema (7.2%), Bullous Pemphigoid (6.3%) and miscellaneous (7.6%) [44]. Further studies also confirm the prevalence of TPMT testing among gastroenterologists (probably due to higher number of patients taking the drug, even though their national guidelines do not recommend the test), followed by dermatologists and rheumatologists [45].

Service provision is as follows: once a TPMT test is requested by a clinician, the patient signs a consent form and a sample is sent to one of the reference laboratories. The laboratory sends a report back within 6 working days, with a narrative interpretation, in which they assign a high or low risk of myelotoxicity and warn of the need for cautious use of AZA or 6-MP:

- Low risk: the patient is normal (his/her TPMT levels are normal or even higher than normal)
- Higher risk than normal (TPMT levels are low) and azathioprine should be taken with caution (clinicians often reduce the dose by half).
- High risk (levels of TPMT are very low or non-existent) and should not be given azathioprine.

The report is only a recommendation that the clinician has to evaluate on the basis of other factors.

In clinical terms, some of the claims in favour of the test sustain that testing is not expensive compared to its benefits, not only for patients who have low or no TPMT levels and should not be taking the drug, but also for patients with intermediate levels, who could benefit from a reduction in the AZA dose. Reference laboratories suggest that TPMT testing is cost-effective on the basis of a prevention of serious ADRs whose treatment costs are very high. Some clinicians, on the other hand, do not agree with this statement, claiming that, in particular in the treatment of ALL, ADRs are detected very quickly as patients undergo very regular blood and liver function tests as well as electrolyte analysis. In response to this, reference laboratories argue that by the time an ADR is detected through routine standard care, the bone marrow may have already suffered a large amount of damage with fatal consequences for the patient.

Some studies have shown that the TPMT enzyme test is cost-effective [40, 44, 46]. However, the interpretation of the empirical evidence remains controversial and neither of the studies was considered when making the final decision on whether TPMT should be implemented across the UK. As a result, TPMT testing is only used locally, through local pre-screening policies, on the basis of the evidence available and the willingness of the NHS Trust to pay for the test.

However, the clinical implementation of TPMT testing in dermatology and haematology (as part of the ALL 2003 clinical trial), and its partial implementation in rheumatology, means that TPMT testing is not used systematically by NHS Trusts. Since NICE had not appraised it and TPMT testing is not reimbursed by the NHS, a decision has to be made by the NHS Trust or a particular clinical department within the NHS Trust as to whether they want to cover the cost of the test. Some hospitals in the UK (the minority – approximately 20 NHS Trusts) have established TPMT pre-screening policies, meaning that they have implemented TPMT testing and cover the cost of the test.

NHS Trusts are the UK health purchasing unit, a system which was introduced to improve access to health services. However, this system sometimes (particularly when there is not an harmonized policy across the NHS) resulted in differences in management and inequalities of access to some health services [47] as it is exemplified in the case of TPMT testing.

Local decisions on TPMT testing depend on the cash balance of the Trust as well as on other factors such as the clinician's willingness to prescribe the test (which often depends on their personal experience of it), or their proximity to a testing laboratory.

In the future, whether the demand for testing increases will depend on the results of future prospective randomized controlled trials, cost-efficiency studies, professional lobbying as well as on NICE willingness to consider new evidence provided related to "non-innovative" off-patent drugs.

#### *A. 6.3 NICE Guidance, is it always an indicator of Good Medical Practice?*

As we have seen through the TPMT case, the diffusion of medical innovation occurs in a conflict-ridden environment, dominated by clash of opinions between clinicians, patients, policy-makers and regulators. NHS reimbursement policies depend simultaneously on clinical guidelines, peers' opinion and NHS budgets and the aims of the three do not always coincide. In this situation, it is difficult to establish good standards of clinical practice, particularly when drugs are not appraised by the main UK reimbursement agency.

Professional guidelines are strong drivers for technology adoption, for this reason, TPMT testing attracted the interest among some clinical groups. The British Association of Dermatology was the first group to recommend TPMT testing [38]; in contrast, the British Society of Gastroenterology has never considered establishing testing recommendations [48].

For ALL the situation is different again. Every child diagnosed with ALL enters into a clinical trial, the UK ALL 2003 [49], in which TPMT testing is undertaken as part of the trial protocol to assess optimal treatments for the disease. Haematologists treating ALL patients refer them for a TPMT test, although clinical opinions about its benefits vary. While some haematologists consider the test to be worthwhile, others think that it serves to detect an ADR that could be detected through routine blood monitoring (after the patient had taken AZA), because TPMT testing does not yet replace a full blood count and electrolyte analysis.

In this context, it is not clear whether experiencing a severe ADR as a consequence of taking AZA, when testing had not been carried out, would be considered to be malpractice. While clinical peer opinion is a strong driver for technology adoption, the lack of consensus about the benefits of TPMT testing across specialties makes the dilemma even more complicated.

## VII. TPMT TESTING: WHAT'S MISSING?

If previous sections illustrated the existing mismatches between policy and practice around the use of TPMT testing, mainly due to regulatory gaps; the following sections will address existing gaps that will need to be better understood in order to define a more harmonized TPMT testing policy across the NHS.

### *a. The Underpinning Science*

Phenotyping or measuring TPMT enzyme levels in blood seems to be the best way of measuring the potential risk of suffering myelosuppression caused by 6-MP and AZA. The enzyme assay gives more information about the risk of suffering ADRs than the genetic assay, which only looks at the most common polymorphisms that affect drug response. Not all the polymorphisms that influence drug response are known and even if they were, doing a genetic analysis of all of them would be too costly and too lengthy. For this reason, genotyping remains an option when phenotyping does not give a conclusive indication.

TPMT is a gene situated in chromosome 6 that contains 23 known polymorphisms (or variations in the DNA) (see Figure 2). Each of these would have a normal, a heterozygous and a homozygous profile. But from these 23, the ones that appear most frequently among the population are polymorphisms on the alleles<sup>1</sup> TPMT \*3A (a combination of \*3B and \*3C), \*2 and \*3C (dominant in black races and Asians). There is also evidence that mutations in other genes, such as the MTHFR (Methylenetetrahydrofolate reductase), may also affect the response to thiopurines [50] and this may be another factor to consider for future service delivery. However, it is still not clear how each influences drug response, only which are the most common ones (\*3A, \*2 & \*3C).

Also, there are environmental factors that influence gene expression. Drug response, apart from having a genetic component, is influenced by general health, gene-gene interactions and drug-gene and drug-drug, interactions. So adverse reactions might appear because of a genetic predisposition, but also because of behavioral conditions that may expose an individual to mutagenic agents and this is something that needs to be integrated into any further PGx analysis.

## FIGURE 2

### *b. Unresolved Regulatory and Patenting Issues*

TPMT testing, in the UK, is delivered in the form of “home-brew” or laboratory developed TPMT tests (LDTs). These are non-patented assays carried out in an NHS accredited laboratory, mixing reagents and following protocols. In contrast to IVD tests, they are not regulated by the IVD Directive, which rules all patented diagnostics.

Public health care systems, such as the NHS, are likely to favour the use of “home-brew” tests (where available), instead of commercial IVD tests. These are often cheaper since they do not have the associated costs of undertaking clinical trials and patenting. As an example, commercial TPMT phenotyping and genotyping in the US (offered by Prometheus) costs \$300 each. The cost in the UK is less than £30 per sample (phenotyping and/or genotyping) [51].

The problem with “home-brew” tests is that, if another company owns the property rights for a specific test similar to the “home-brew”, the company could ban the laboratory from doing a similar test, or sell the commercial license to a laboratory.

Patent protection is a strong driver for private companies to develop IVDs [52]; however, one of the fears about patenting genetic tests is that it might limit access to whoever is willing to pay [53]. TPMT “home-brew” testing has not faced any legal battle in the UK (where a commercial version is not available); however, in 2009, Prometheus filed a law suit against the Mayo Clinic for the infringement of the patent for TPMT testing.

## VIII. DIFFUSION OF INNOVATION IN A HIGHLY REGULATED SPHERE

One of the biggest challenges of medical innovation is its high degree of control both during development and delivery. Drug regulatory agencies need to grant market approval for drugs, tests and medical devices and then, justify their health need and cost-benefit before being implemented and reimbursed.

Regulations, when they exist, are a critical hurdle for diffusion of medical innovations. The case of TPMT testing presented here shows how regulations in the case of pharmacogenetics and personalised medicine for off-patent drugs lag behind implementation.

### *A. Figures*

<sup>1</sup> Alleles are used to define a specific DNA sequence or physical space inside a gene. Variations in an allele are defined as polymorphic variants of the allele or genetic polymorphisms.



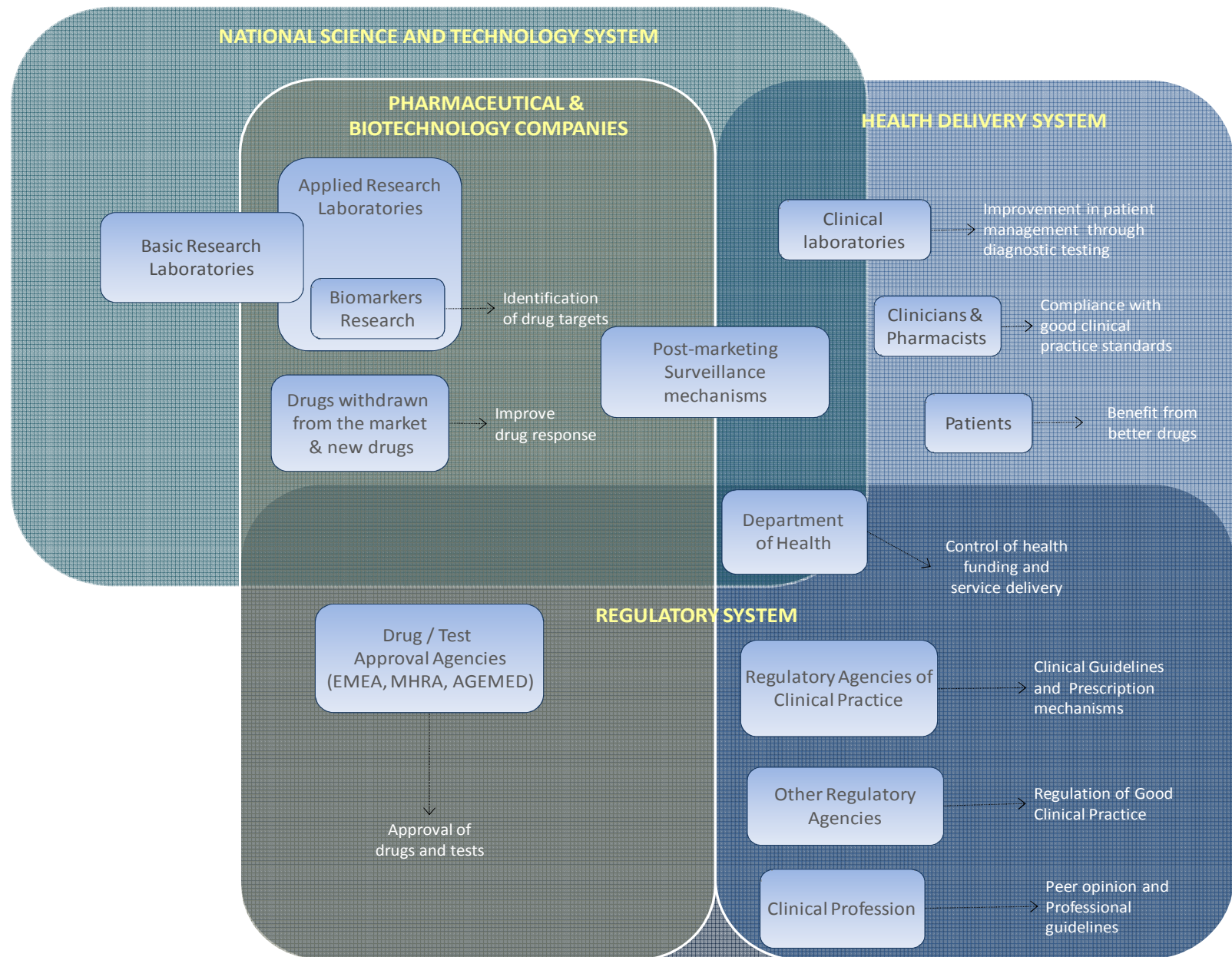


Figure 1. Representation of the socio-technical system in which PGx is embedded

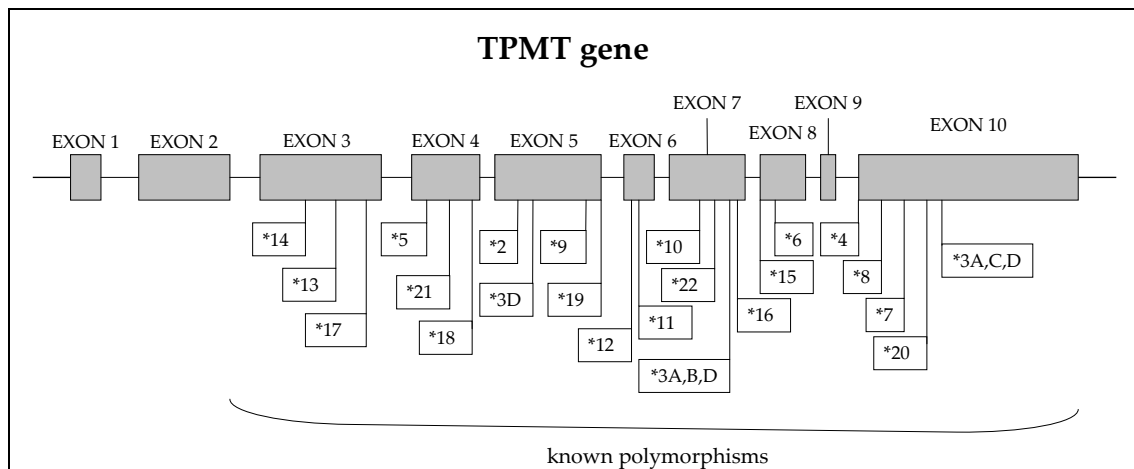


Figure 2: Representation of the TPMT gene, with all the regions where genetic polymorphisms may be found. Each of these regions can then have three different allelic variants: homozygous for "Low" TPMT levels, heterozygous and homozygous for "High" TPMT levels. Exons are the functional parts of a gene as opposed to introns, which are not functional).

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